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Use of xenon as a sedative for patients receiving critical care*

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Objective: Many sedative regimens are used in the intensive care setting, but none are wholly without adverse effect. Xenon is a noble gas with sedative and analgesic properties. It has been used successfully as a general anesthetic and has many desirable properties, not least of which is a minimal effect on the myocardium. In theory, xenon may provide sedation without adverse effect for certain groups of critically ill patients. The objective of this study was to assess the feasibility of using xenon as an intensive care sedative.

Design: Double-blind, randomized study.

Setting: Tertiary-level intensive care unit.

Subjects: Twenty-one patients admitted to an intensive care unit following elective thoracic surgery.

Interventions: A standard intensive care sedation regimen (intravenous propofol at 0–5 $mg \cdot kg^{-1} \cdot hr^{-1}$ and alfentanil 30 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) was compared with a xenon sedation regimen delivered using a novel bellows-in-bottle delivery system.

Measurements and Main Results: Each sedative regimen was continued for 8 hrs. The hemodynamic effects, additional analgesic requirements, recovery from sedation, and effect on hematological and biochemical variables were compared for the two sedation regimens. All patients were successfully sedated during the xenon regimen. The mean ± SD end-tidal xenon concentration required to provide sedation throughout the duration of the study was 28 ± 9.0% (range, 9–62%). Arterial systolic, diastolic, and mean pressures showed a greater tendency for negative gradients in patients receiving the propofol regimen ($p < .05$, $p < .1$, and $p < .01$, respectively). Recovery following xenon was significantly faster than from the standard sedation regimen ($p < .0001$). Hematological and biochemical laboratory markers were within normal clinical limits in both groups.

Conclusions: Xenon provided satisfactory sedation in our group of patients. It was well tolerated with minimal hemodynamic effect. Recovery from this agent is extremely rapid. We have demonstrated the feasibility of using xenon within the critical care setting, without adverse effect. (Crit Care Med 2003; 31:2470–2477)

Key Words: noble gases; sedatives; critical care

Modern intensive care units have changed significantly since their inception during the polio epidemics of the 1950s. It was during this period that anesthetic agents were used as sedatives, initially to facilitate the removal of tracheal secretions. It was immediately apparent that when these agents were used in critically ill patients, the adverse effects of the agents would be greatly increased. Although many sedative regimens presently are used, intensive care still remains an unpleasant experience for many patients (1). No currently used regimen is totally free from adverse effects. Midazolam, alfentanil, and propofol, given by intravenous infusion, form the mainstay of current clinical practice in the United Kingdom (2). Inhaled anesthetics have been used successfully in the critical care setting (3), but their use is not common. Isoflurane, a methyl ethyl ether, is advocated for a number of applications, most importantly, the sedation of brittle asthmatics (4), but this remains a niche application.

The pharmacokinetics of even the commonly used intravenous anesthetics remain uncertain in the critically ill, and all existing intravenous drugs carry the risks of cumulation and cardiovascular depression, especially in patients with multiple organ dysfunction. Recently, the safety of prolonged, high-dose infusions of propofol has been questioned in both children (5) and adults (6).

Xenon is a noble gas with sedative and analgesic properties. It is for all intents and purposes chemically inert and has been successfully used as a general anesthetic. It has many desirable properties not least of which is a minimal effect on the myocardium (7). It has been shown to provide pleasant, well-tolerated sedation in volunteers (8). Xenon has not become established in modern anesthetic practice due to its relatively low potency and its expense (9). Its pharmacokinetic and pharmacodynamic properties are close to those of an "ideal" sedative, and it is exhaled by the lungs unchanged, a highly desirable property in the patient with hepatic or renal impairment. Having the lowest blood gas solubility of any anesthetic gas (10) means that its effect and recovery profile are both rapid (11). In theory, xenon may provide sedation without adverse effect for certain groups of critically ill patients.

We report the first use of xenon as an intensive care sedative. The primary objective of this double-blind, randomized study was to assess the feasibility of using xenon for this purpose. We used a closed circuit breathing system especially designed for use in the intensive care unit and studied a group of relatively low-risk

*See also p. 2556.

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Supported, in part, by BOC Gases (UK), which supplied the xenon for this study, and by a Fellowship Award from the Association of Anaesthetists of Great Britain and Ireland (1999–2000) (AB).

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patients who were capable of giving informed consent before elective admission to the intensive care unit.

METHODS

Following local Research Ethics Committee approval and written informed consent, 21 patients requiring mechanical ventilation after elective thoracic surgery were studied using a randomized, crossover design. These patients, admitted electively to the intensive care unit, were able to give written informed consent before surgery. Patients with a history of epilepsy or evidence of hepatic or renal dysfunction were not studied. The Acute Physiology and Chronic Health Evaluation II score was measured at admission to the intensive care unit in accordance with standard practice.

Following consent, the subjects were randomized into one of two groups as part of a crossover study: group A (n = 10) and group B (n = 11). Thirty minutes before the anticipated end of surgery, anesthesia was maintained with isoflurane in oxygen. At admission to the intensive care unit, patients were stabilized and then allocated to one of two sedative regimens. Group A received a standard sedation and analgesia regimen using intravenous propofol (2%) at 0–5 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$ and alfentanil 30 $\mu g{\cdot}kg^{-1}{\cdot}hr^{-1}$ for 8 hrs. These drugs then were stopped, and the time taken for the patient to begin to appear restless (Ramsay score 1) to a blinded observer was noted (12). Sedation then was recommenced using variable concentrations of xenon in oxygen-enriched air as required. Patients in group B (the other limb of the crossover trial) initially were sedated using the xenon in oxygen-enriched air regimen for 8 hrs. After this period, the sedation was stopped and as in group A the patient's conscious level allowed to increase. The alternate regimen of propofol and alfentanil then was begun and continued for 8 hrs.

Additional analgesia was provided in both groups (when required) at the request of the attending nurse or physician, who was blinded to the sedation regimen, according to normal clinical practice, using boluses of alfentanil 250 μg. If more than six boluses were needed in any 1-hr period, then an infusion of alfentanil was begun at a rate equivalent to the previous hour's requirement.

An unblinded clinician—at the request of a nurse who was blinded to both sedative regimens—administered all sedatives and analgesics. The nurse providing care of the patient was instructed to order an increase in sedation to ensure that the patient had a Ramsay sedation score (12) of either 2 or 3. If the nurse believed that the patient was in pain, despite adequate sedation, if pain was preventing adequate sedation, or if the patient communicated to the nurse that he or she was sore, the nurse instructed additional analgesia to be administered by the unblinded operator. A physician, unaware of the ongoing sedation regimen, administered inotropes, fluids, blood, and other drugs according to the patient's requirements. To ensure blinding of the observers, the xenon delivery system remained unchanged in appearance throughout the study. The addition of xenon to the closed-circuit breathing system was not visible to the caregivers. The concentration of xenon delivered was monitored using a calibrated thermal conductivity meter that was only seen by the operator and not the attending physician or the nursing staff. The alternate sedation regimen (the propofol/alfentanil regimen) was replaced by a placebo infusion of Intralipid and saline to ensure that the appearance of both sedation regimens (to all except the sedation operator) was identical.

The patient's lungs were ventilated using a Bennett Puritan ventilator and a bellows-in-bottle breathing interface (13). This system operated as a balanced, closed-circuit breathing system driven by a conventional intensive care ventilator. The ventilatory modes of positive end-expiratory pressure, continuous positive airway pressure, and synchronized intermittent mandatory ventilation were applied as deemed clinically necessary. All measurements of both airway pressure and changes in inspiratory pressure required to initiate ventilation were made by the Puritan Bennett 7200A ventilator as normal. The bellows-in-bottle interface did not alter the performance of the ventilator. Once balanced, the system automatically replaced oxygen uptake from the circle with oxygen from the driving ventilator (Figure 1). Aliquots of xenon were added through a one-way valve by an unblinded operator to achieve the level of sedation directed by the blinded observer. The end-tidal concentrations of carbon dioxide and oxygen concentration were monitored continuously using an infrared gas analyzer (Datex Capnomac, Datex) and the ventilatory rate and tidal volume adjusted as appropriate to maintain an end-tidal carbon dioxide concentration between 4% and 6%. The end-tidal concentration of xenon was monitored using a calibrated thermal conductivity monitor (Bedfont Scientific, UK). Patients were monitored noninvasively using a pulse oximeter and electrocardiograph. Each patient also had a radial arterial cannula and a pulmonary artery flotation catheter inserted for hemodynamic monitoring. Pulmonary artery occlusion pressure, mixed venous oxygen saturation, and cardiac output were recorded at 30-min intervals. The following were measured at admission to intensive care and at the end of each sedative regimen: hemoglobin concentration, white cell count, platelet count, activated partial thromboplastin time, prothrombin time, arterial blood lactate, plasma epinephrine and norepinephrine, and blood urea and electrolytes.

Statistical Analysis. The data from the xenon sedation regimen (regimen X) from groups A and B were pooled for analysis and compared with the pooled propofol/alfentanil sedation regimen data (regimen P) from groups A and B. Alfentanil requirements were compared using Wilcoxon matched pairs signed-ranks testing (nonparametric). For comparison of the cardiovascular variables, the first 60 mins of each sedative regimen was excluded from analysis to ensure an adequate washout. The effects of each sedation regimen on hemodynamic variables over the entire sedative period were examined using linear regression modeling and an examination of the

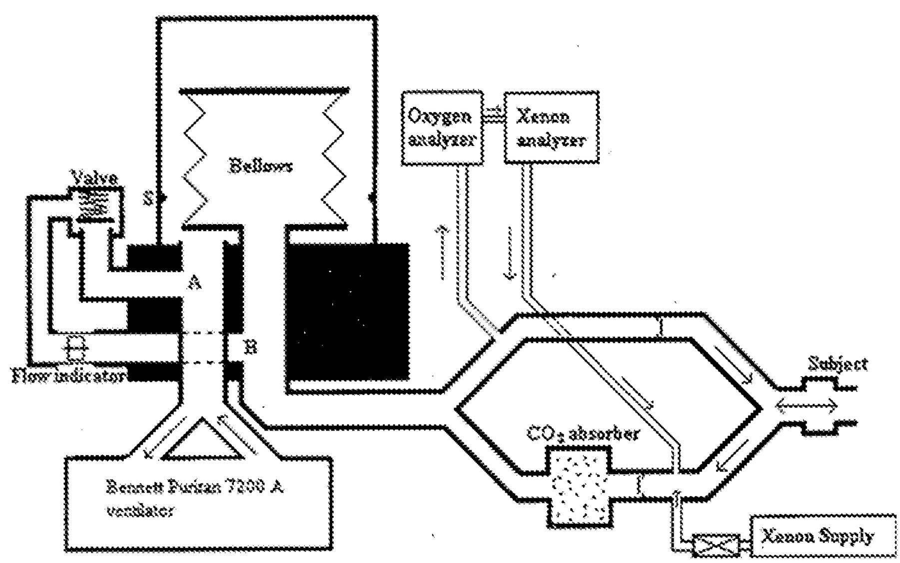

Figure 1. Diagrammatic cross section of the bellows-in-bottle interface.

trends for each variable and each individual patient. The times taken for each patient to achieve a Ramsay sedation score of 1, after each sedation regimen was stopped, were compared using Wilcoxon signed rank testing.

The sample size of the study was estimated using means and standard deviations from a previous study (14). It was based on detecting a difference in systolic blood pressures of 15%, accepting a power of 90% ($p < .05$).

RESULTS

Fifteen men and six women (American Society of Anesthesiologists class III) requiring elective ventilation following thoracotomy were studied. The median age was 63 yrs (range, 39–80 yrs), and median Acute Physiology and Chronic Health Evaluation II score at admission to intensive care was 24 (range, 14–31). All patients were successfully sedated during the xenon regimen. The mean (SD) end-tidal xenon concentration (%) required to provide sedation throughout the duration of the study was 28 (9.0) (range, 9–62). The concentration of xenon required for sedation just before its administration was discontinued, and the range of concentrations required throughout the study is shown for each patient in Figure 2. The mean Ramsay sedation scores and mean bispectral indexes, measured at 30-min intervals, were similar during both sedative regimens (Table 1).

The mean (SD) amount of propofol delivered in regimen P was 4.5 (2.1) $mg \cdot kg^{-1} \cdot hr^{-1}$. In regimen P, the mean (SD) alfentanil delivered to each patient was 28.0 (10.0) $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The total alfentanil administered to individual patients in each group is shown in Figure 3. The total alfentanil, expressed as mean (SD), used in regimens X and P was 4.5 (3.2) mg and 15.2 (3.4) mg, respectively.

Linear regression and examination of trends in arterial systolic, diastolic, and mean pressures showed a greater tendency for negative gradients in patients receiving regimen P ($t = 2.24$, $p < .05$; $t = 1.74$, $p < .1$; $t = 2.84$, $p < .01$, respectively; Table 2). The pooled data for arterial blood pressures in each regimen (mean and SD) are also shown in Figure 4. Cardiac index increased in the first 8 hrs of sedation irrespective of sedative regimen (Fig. 5). There was no significant difference in cardiac index during the second period of sedation between either sedative regimen. Mean heart rate was lower in the first 2 hrs of xenon administration (regimen X) compared with the standard sedation regimen (regimen P), but this decrease was not statistically significant. Systemic vascular resistance index decreased throughout the study during both sedative regimens. There was no significant effect of sedation regimen on this decrease (Table 3). The pulmonary vascular resistance index, systemic vascular resistance index, and pulmonary artery occlusion pressure are shown in Table 3. The mean mixed venous oxygen saturation was significantly higher in the xenon regimen during the last 2 hrs of sedation (Fig. 6).

There were no significant between-group differences. The arterial oxygen saturation was similar and well maintained in both groups throughout the study (Table 3). The times taken for each patient to achieve a Ramsay sedation score of 1 after each sedation regimen was stopped were significantly shorter following the xenon sedative regimen (Table 4). Hematological and biochemical laboratory markers were within normal clinical limits in both groups and not significantly altered by xenon sedation. Catecholamine concentrations did not differ significantly between groups (Tables 5–8).

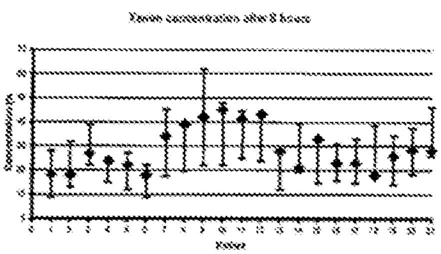

Figure 2. The xenon concentration (percentage) required for sedation in each patient after 8 hrs of xenon administration. Error bars represent the range of concentrations delivered to each patient during the xenon regimen. These are pooled data from both groups A and B, the two arms of a randomly allocated crossover trial.

DISCUSSION

Modern anesthetic agents are so safe that in all but the most critically ill patients there may be little to be gained by using xenon as a general anesthetic. The situation is different in intensive care, where sedation regimens may be employed for days or weeks. This is the first report of an inert gas being used as a sedative in intensive care, and this study demonstrates the feasibility of providing sedation with xenon.

Xenon's reported lack of effect on the myocardium, cardiac index, arterial blood pressure, and vascular resistance (7, 15, 16) makes it theoretically attractive for sedation of the critically ill. This contrasts with the well-known myocardial depressant effects of propofol. Our study reports that decreases in blood pressure were less in the xenon regimen than in the propofol regimen. Marked changes in the cardiovascular system occur in the first 16 hrs following thoracic surgery, and compensatory physiologic mechanisms may be of greater significance than the choice of sedative agent. Thus, the

Table 1. Mean (SD) Bispectral Index (BIS) and Median (Interquartile Range) Ramsay Sedation Score for Xenon (X) and Propofol (P) Regimens at 30-min Intervals During Each Sedative Regimen

	Regimen X		Regimen P	
Time, Mins	BIS	Ramsay Score	BIS	Ramsay Score
0	67.1 (20)	4 (3–5)	64.0 (19)	4 (3–5)
30	61.2 (18)	3 (3–5)	64.0 (20)	4 (3–4)
60	65.7 (22)	3 (3–5)	67.8 (19)	4 (3–4)
90	65.0 (19)	3 (3–4.5)	68.6 (21)	4 (4–4)
120	64.4 (21)	3 (3–4.5)	66.0 (19)	4 (3–4)
150	64.7 (19)	3 (2.5–4)	68.5 (20)	3 (2.5–4)
180	65.0 (20)	3 (3–4)	70.2 (19)	4 (3–4)
210	61.7 (19)	3 (2.5–3.5)	60.6 (18)	4 (3–4)
240	67.7 (21)	3 (3–4.5)	64.0 (19)	4 (3–4)
270	62.4 (20)	3 (3–4)	66.7 (19)	3 (2.5–4)
300	61.2 (19)	3 (3–4.5)	65.6 (22)	3 (3–4)
330	61.9 (23)	3 (2–4)	66.9 (16)	3 (3–4)
360	63.0 (20)	3 (3–4)	69.7 (20)	3 (3–4)
390	66.5 (22)	3 (2.5–4)	69.5 (20)	3 (2.5–4)
420	59.6 (20)	3 (2.5–4)	69.6 (20)	3 (2–4)
450	62.9 (16)	4 (3–4)	70.0 (19)	3 (2–3.5)
480	57.9 (19)	3 (3–4)	70.9 (20)	3 (2–3.5)

Data are pooled from both arms of the crossover study ($n = 21$).

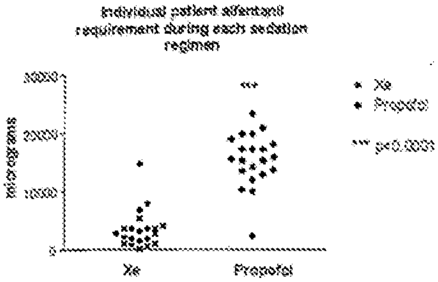

Figure 3. The total alfentanil (micrograms) delivered to each patient during the xenon (*Xe*) and propofol sedation regimens. Dots and squares represent individual patients. The total amount of alfentanil used was significantly less during sedation with xenon ($p < .0001$). Data are pooled from both arms of the crossover study ($n = 21$).

Table 2. Mean (SD) Systolic, Diastolic, and Arterial Blood Pressures at 30-min Intervals During Administration of Xenon (X) and Propofol (P) Regimens

	Arterial Systolic Blood Pressure		Arterial Diastolic Blood Pressure		Arterial Blood Pressure	
Time	X	P	X	P	X	P
0	128 (27)	130 (25)	68 (12)	69 (9)	90 (17)	93 (14)
30	129 (25)	127 (24)	67 (13)	69 (8)	88 (16)	91 (12)
60	129 (25)	120 (18)	67 (10)	66 (9)	88 (15)	87 (11)
90	132 (23)	126 (25)	70 (11)	67 (10)	92 (14)	89 (15)
120	136 (24)	126 (26)	70 (11)	66 (8)	94 (15)	87 (13)
150	139 (31)	124 (21)	71 (10)	66 (10)	95 (16)	86 (12)
180	132 (27)	123 (21)	69 (13)	65 (9)	92 (17)	86 (13)
210	133 (27)	122 (24)	69 (10)	65 (10)	93 (14)	85 (14)
240	129 (29)	118 (22)	68 (12)	63 (11)	92 (17)	84 (13)
270	124 (18)	118 (20)	66 (9)	63 (11)	88 (10)	82 (14)
300	132 (27)	116 (21)	68 (14)	63 (9)	91 (18)	82 (11)
330	139 (26)	115 (21)	72 (16)	61 (9)	96 (18)	79 (11)
360	133 (26)	117 (19)	71 (13)	61 (9)	94 (17)	80 (12)
390	134 (26)	114 (20)	69 (12)	61 (8)	93 (16)	79 (11)
420	135 (25)	118 (23)	70 (11)	64 (10)	94 (16)	83 (14)
450	134 (24)	118 (17)	69 (12)	62 (9)	92 (16)	81 (10)
480	136 (22)	116 (18)	69 (10)	61 (8)	93 (13)	79 (10)

Data are pooled from both arms of the crossover study, groups A and B ($n = 21$).

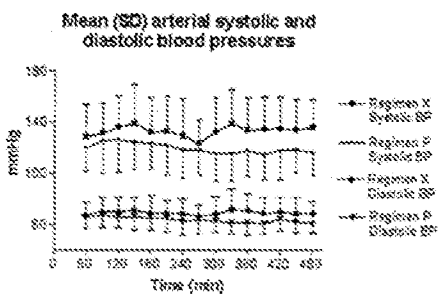

Figure 4. Mean (SD) arterial systolic and diastolic blood pressures (*BP*) measured at 30-min intervals in both sedative regimens, xenon (*X*) and propofol (*P*). Data are pooled from both arms of the crossover study ($n = 21$).

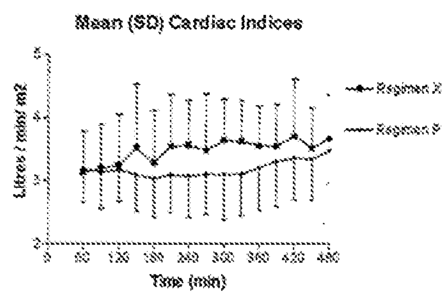

Figure 5. Mean (SD) cardiac index measured at 30-min intervals in both sedative regimens. Data are pooled from both arms of the crossover study ($n = 21$).

beneficial effects of xenon on myocardial contractility, if any, may too subtle to be seen in the context of rewarming and recovery from prolonged anesthesia. It may be that in this group of patients with myocardial function capable of responding to the challenges of the postoperative period, there is no benefit to be gained by using xenon as the sedative agent. However, xenon appears to offer marginally greater cardiovascular stability during the first 8 hrs of therapy in the intensive care unit than the standard sedative regimen. Clearly in states of sepsis or other forms of shock, it is essential to reduce the risk of myocardial depression and hypotension; xenon may have a niche role in such circumstances.

The effects of sedation and analgesia can be difficult to separate in the clinical environment. The analgesic properties of xenon have been well reported. In volunteers, subanesthetic fractions of xenon and nitrous oxide produce a similar and useful analgesic effect (0.3 MAC of xenon and nitrous oxide) (17) and analgesia to ischemic, electrical, and mechanical stimulation (18). At 1 MAC the fentanyl requirements of patients undergoing surgery are dramatically reduced when compared with nitrous oxide, and many patients receiving anesthetic concentrations of xenon require no opioid analgesia whatever (7, 9). The potent analgesic properties of xenon are again demonstrated by this study in the context of critical care. Alfentanil requirements were minimal in all except one patient during sedation with xenon. One subject had equivalent alfentanil requirements during both regimens, and this raises the possibility that, like the opioids, the analgesic effects of xenon may show considerable interpatient differences. By using xenon as a single agent for sedation and analgesia, it may be possible to avoid some of the problems of multiple sedative and analgesic infusions.

As a naturally occurring gas, xenon has not been subjected to the rigorous preclinical safety testing that the modern clinically used sedatives have been subjected to. Prolonged exposure to xenon in either anesthetic or subanesthetic concentrations has not been reported in humans. Although highly unreactive chemically, this inertness does not guarantee biological safety, and xenon is certainly not biologically inert. In addition to its potent anesthetic and analgesic effects, xenon has an action at the *N*-methyl-D-aspartate receptor (19) and has been shown to inhibit Ca^{2+}-regulated transitions in human endothelial cells and arrest the division of rat astrocytes in metaphase (20, 21). The analysis of routine biochemical and hematological tests in this study, while not proving the safety of prolonged exposure to xenon, adds to our existing knowledge on the subject. A reduction in circulating epinephrine concentrations during xenon administration has been reported in studies comparing Xe with N_2O and a total intravenous regimen (7, 22). No differences in plasma catecholamine concentrations were seen between the two sedative regimens in our study. The extent and severity of surgery may well have been an insurmountable stimulus in this case.

A change in Ramsay sedation score is a crude and subjective assessment of offset of sedative effect, but nevertheless there were marked differences between regimens. We report an emergence time from sedation less than one third that of a

Table 3. Range of Arterial Oxygen Saturation (Sp_{O_2}), mean (SD) Systemic Vascular Resistance Index (SVRI), Mean (SD) Pulmonary Vascular Resistance Index (PVRI), and Median (Interquartile Range) Pulmonary Artery Occlusion Pressures (PAOP) for Xenon (X) and Propofol (P) Regimens at 30-min Intervals

	Sp_{O_2}, %		SVRI, Dynes · sec/cm^5		PVRI, Dynes · sec/cm^5		PAOP, mm Hg	
Time, Mins	X	P	X	P	X	P	X	P
0	96–100	99–100	2031 (698)	2208 (673)	276 (101)	293 (125)	7 (6–10.5)	7 (5.5–10)
30	96–100	98–100	2053 (673)	2380 (486)	313 (125)	294 (104)	8 (6–10)	7 (6–10)
60	96–100	97–100	2115 (639)	2082 (573)	314 (97)	265 (96)	8 (6–10.5)	7 (6–10.5)
90	93–100	96–100	2126 (739)	2177 (517)	350 (119)	290 (104)	9 (6.5–11)	8 (5.5–9.5)
120	96–100	94–100	2222 (733)	1993 (594)	336 (112)	270 (131)	9 (7–11)	7 (5–11)
150	96–100	97–100	2083 (714)	2013 (562)	326 (125)	266 (131)	8 (7–10)	8 (6–9)
180	96–100	98–100	2107 (714)	2133 (498)	362 (127)	280 (106)	9 (7.5–11)	7 (5–9)
210	95–100	97–100	1970 (464)	2030 (469)	313 (121)	259 (112)	9 (6.5–10.5)	8 (5–9)
240	96–100	97–100	2517 (483)	1960 (448)	312 (142)	262 (93)	9 (7–11.5)	7 (3.5–8.5)
270	96–100	97–100	1913 (510)	1892 (379)	329 (125)	253 (142)	10 (8–11.5)	7 (4–9.5)
300	96–100	96–100	1846 (679)	1980 (505)	305 (104)	272 (137)	9 (7–11.5)	7 (5–9)
330	97–100	95–100	2009 (635)	1922 (534)	301 (122)	232 (96)	9 (7–12)	7 (3.5–9)
360	96–100	96–100	1949 (581)	1871 (524)	333 (88)	259 (97)	10 (7.5–12.5)	7 (5–8)
390	97–100	95–100	1970 (591)	1856 (485)	317 (116)	272 (120)	10 (6.5–11.5)	7 (5.5–10)
420	96–100	95–100	1906 (625)	1857 (559)	324 (105)	268 (113)	10 (7.5–11.5)	6 (5.5–10)
450	97–100	96–100	1948 (509)	1869 (497)	312 (133)	271 (135)	9 (7–12)	7 (5.5–9.5)
480	98–100	96–100	1912 (474)	1749 (416)	281 (84)	223 (95)	9 (7.5–12.5)	7 (5–8.5)

Data are pooled from both arms of the cross-over study (n = 21).

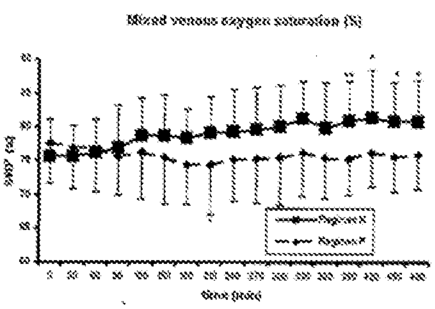

Figure 6. Mean (SD) mixed venous oxygen saturation (SVO_2) measured at 30-min intervals in both sedative regimens, xenon (*X*) and propofol (*P*). Data are pooled from both arms of the cross-over study (n = 21). *$p < .05$, **$p < .01$.

Table 4. Mean (SD) Times Taken for Patients to Emerge to Ramsay Sedation Score of 1 After Discontinuation of Xenon (X) and Propofol (P) Regimens

	Xenon Regimen	Propofol Regimen
Time, secs	173 (114)^a	574 (278)

^{a}$p < .0001$. Data are pooled from both arms of the cross-over study(n = 21).

Table 5. Mean (SD) pH, Pa_{O_2}, Pa_{CO_2}, Base Deficit, and Blood Lactate Following Xenon and Propofol Regimens

	pH	Pa_{O_2}, kPa	Pa_{CO_2}, kPa	Base Deficit	Lactate, mmol·mL^{-1}
Post-xenon	7.37 (0.1)	26.5 (15)	4.9 (0.7)	3.3 (3.8)	1.5 (0.7)
Post-propofol	7.39 (0.1)	18.8 (8)	4.6 (0.5)	3.3 (2.9)	1.5 (0.8)

Data are pooled from both arms of the crossover study (n = 21).

Table 6. Mean (SD) Hemoglobin, White Cell Count (WCC), Platelet Count, Prothrombin (PT) Time, Activated Partial Thrombin Time (APTT), and Fibrinogen Following Xenon and Propofol Administration

	Hb, g·dL^{-1} (Hb)	WCC	Platelets, $\times 10^{-3}$, μL^{-1}	PT, secs	APTT, secs	Fibrinogen, g·L^{-1}
Post-xenon	11.2 (1.7)	10.3 (4.8)	168 (56)	15.3 (2)	36.9 (6)	3.1 (0.8)
Post-propofol	11.1 (1.6)	10.5 (3.6)	165 (44)	15.2 (1)	34.4 (2)	2.9 (0.7)

Data are pooled from both arms of the crossover study (n = 21).

standard intravenous regimen. Both agents were titrated to equal clinical effect. Although the bispectral indexes appear slightly lower in the xenon group, there were no statistical differences between the sedative regimens. It has become apparent that the bispectral index recorded during xenon administration does not correlate with sedation or arousal in a manner similar to propofol (23). This is not surprising given the different mechanisms of action of each agent. Such a rapid recovery from the effects of xenon sedation may facilitate the assessment of head-injured patients in whom an accurate assessment of the true neurologic state (in the absence of sedative effect) is highly desirable. The effects of brief periods of xenon inhalation in head-injured patients, at concentrations used to enhance computed tomography scan of the brain, have been studied. In 13 patients with an acute head injury, Plougmann et al. (24) reported an increase in intracranial pressure in all patients with a resultant decrease in cerebral perfusion pressure in eleven. The authors also reported that in this study (examining a 20-min period of xenon inhalation), the effects of xenon were most marked during the first 5 or 6 mins and were probably analogous to those seen during induction of anesthesia. Importantly, no signs of cerebral oligemia or ischemia were seen in the measured arteriovenous oxygen saturation difference. In another study of 23 comatose patients, inhalation of 32% xenon did not cause a significant increase in intracranial pressure (25). Changes seen in this study in individual patients' intracranial pressure were ascribed to alterations in arterial CO_2. This preservation of cerebral reactivity in response to arterial CO_2 during xenon inhalation also was reported by Plougmann et al. (24). In an earlier study of mechanically ventilated patients re-

Table 7. Mean (SD) Serum Sodium (Na^+), Potassium (K^+), Urea, Creatinine, Calcium (Ca^{2+}), and Bilirubin Following Xenon and Propofol Administration

	Na^+, $mmol \cdot L^{-1}$	K^+, $mmol \cdot L^{-1}$	Urea, $mmol \cdot L^{-1}$	Creatinine, $mmol \cdot L^{-1}$	Ca^{2+}, $mmol \cdot L^{-1}$	Bilirubin, $\mu mol \cdot L^{-1}$
Post-xenon	139 (3)	4.1 (0.4)	4.8 (1)	79 (25)	1.94 (0.2)	16 (6)
Post-propofol	139 (2)	3.8 (0.4)	4.9 (1)	80 (27)	1.86 (0.1)	14 (8)

Data are pooled from both arms of the crossover study (n = 21).

Table 8. Mean (SD) Plasma Adrenaline and Noradrenaline Concentrations ($nmol \cdot L^{-1}$) Following Xenon and Propofol Administration

	Epinephrine	Norepinephrine
Baseline	0.98 (1.1)	3.75 (1.7)
Post-xenon	0.56 (0.2)	4.03 (1.8)
Post-propofol	0.40 (0.43)	3.23 (1.8)

Data are pooled from both arms of the crossover study (n = 21).

ceiving brief periods of xenon to enhance computed tomography scanning, again no significant increase in intracranial pressure was seen (26). The effects on cerebral blood flow and intracranial pressure of prolonged inhalation of xenon at sedative concentrations have not yet been reported, but its use would appear to offer the potential of therapeutic benefit in patients in whom it is necessary to accurately and quickly determine the true neurologic state.

The inhalational route for the delivery of sedative agents has never been as convenient as the intravenous route but has the advantage that the effector site (brain) concentration can be extrapolated with reasonable accuracy from the end-tidal concentration. This allows feedback loops to be established that can automate the adjustment of xenon concentration to a level predetermined by the physician. Once a steady state of a desired concentration of xenon has been achieved within a closed-circuit breathing system (this occurs rapidly), then almost no further xenon expenditure is incurred and cost becomes a lesser issue. The cost per unit time of xenon anesthesia (or indeed, sedation) decreases dramatically after the first 15 mins of administration, and when xenon is used in anesthesia the cost becomes comparable with other anesthetics delivered using a semiclosed breathing system after about 4 hrs (27). The longer the period of administration of xenon, the more cost-effective it becomes. At present, the routine use of a closed-circuit breathing system in intensive care is confined to research studies, but should such a system be required, the technology exists to provide it (13, 28). By using such systems in combination with a xenon recycling system, the cost of sedation can be reduced even further.

Delivery of xenon gas to the patient was achieved using the balanced circle system described by Dingley et al. (29) and shown in Figure 1. Although this functions as a fully closed breathing system, losses of xenon in addition to tissue uptake and redistribution occurred when the carbon dioxide absorbent of this system was changed and also during suctioning of the tracheal tube during physiotherapy. These losses are unavoidable but could be possibly reduced using recycling technology. The manual addition of xenon into the breathing system required a physician/operator to be present during the study and this was believed to be desirable as an additional safety feature, since the attending medical staff were blinded to sedation regimens. Selection and computer control of a set concentration of xenon would also smooth out the peaks and troughs of xenon concentration seen during manual delivery. For future use, an initial end-tidal concentration of xenon could be selected, and this study reports the range of concentrations encountered. Patients requiring high inspired oxygen concentrations would not be suitable for sedation with xenon, but the median fraction of inspired xenon (0.27 in this study) is low enough to allow its use in most patients, except those requiring very high concentrations of oxygen. The prolonged use of closed-circuit breathing systems in intensive care has several caveats not normally given consideration in general anesthesia. The accumulation of foreign gases within a closed breathing system was reported by Versichelen et al. (30). During prolonged closed-circuit anesthesia, acetone may be generated by oxidative metabolism of free fatty acids, and an increased formation is seen in starvation and in decompensated diabetes mellitus.

We have shown that it is feasible to use xenon for intensive care unit sedation and propose that it may have advantages over standard drugs in the sedation of hemodynamically unstable patients such as those recovering from myocardial infarction, endotoxemia, cardiomyopathy, or closed head injury.

A blood concentration >50 mg/L may extend the emergence period from general anesthesia and may contribute to postoperative vomiting. The increase in the acetone concentration during closed-system anesthesia depends on its preoperative value and on the duration of the anesthetic procedure (31). However, such increases are small (1.3–5.9 ppm in the inspired gas of a closed circuit over 4 hrs) and are unlikely to lead to clinical symptoms by themselves (32) (the European Union maximum workplace concentration for acetone is 1000 ppm). During the first 5 hrs of general anesthesia, Strauss and Hausdorfer (31) could not establish a significant difference when comparing the use of closed and semiopen breathing systems. A simple way of decreasing the metabolism of free fatty acids, and hence acetone, would be to ensure that nutritional needs in the critically ill patient were adequately met. Methane generated by bacterial decomposition of intestinal matter is exhaled in small quantities by patients and has been shown to accumulate within closed breathing systems during anesthesia. Methane is nontoxic and its significance is that it is flammable if mixed with oxygen. Such concentrations producing this effect are well above those seen in prolonged closed-system anesthesia (33). Methane may interfere with the interpretation of halothane concentrations by some infrared gas analyzers, but this is of no relevance to intensive care.

Evidence of tolerance to xenon was not formally assessed, although in seven subjects the final concentration of gas inhaled was noted to be at or close to the maximum inspired concentration (Figure 2).

The significantly higher mixed venous oxygen saturations seen during the last 2 hrs of xenon sedation may be due to a combination of the cardiovascular changes. However, although inert biochemically, xenon has been shown to form weak van der Waal's interactions with both hemoglobin and myoglobin (34, 35), and it is possible that the delivery of oxygen to the tissues is affected. The changes in mixed venous oxygen saturation are important; however, given the changes in hemodynamics between the two groups, any proposal that xenon alters the mixed venous oxygen saturation of blood *in vivo* would not be supported by the data presented. The mechanism for these changes is unclear, and further elucidation of this phenomenon was beyond the method of the study, but we hope that this report will inspire further study in this area. After the addition of xenon to the closed circuit, the inspired oxygen fraction decreased (by varying amounts, depending on the amount of xenon added). To compensate for this, the unblinded operator transiently increased the inspired oxygen fraction of the driving gas. The increase in oxygen content of the driving gas may have been higher than necessary (as a safety precaution) and resulted in an overshoot in the desired level of inspired oxygen and therefore the arterial oxygen tension. It is important to note that the arterial oxygen saturations and hemoglobin concentrations (and hence actual oxygen delivery) were similar between the two groups. Because a placebo gas was not added to the closed circuit in place of xenon, this overshoot did not occur in the propofol/alfentanil regimen. The increased Pa_{O_2} in the xenon regimen reflects the inaccuracies in desired gas fractions that result following manual addition of gases to a closed system. Computer-servo control of the addition of xenon to the circuit could prevent such fluctuations in gas content but was beyond the scope of this project.

Avoidance of tachycardia is undoubtedly beneficial in the setting of ischemic heart disease, and we have shown this to be true of xenon during the first 2 hrs of sedation.

CONCLUSIONS

Xenon provided satisfactory sedation in our group of 21 elective thoracic surgery patients. It was well tolerated and had minimal hemodynamic effects, unlike the comparator propofol regimen. We have shown that it is feasible to use xenon for intensive care unit sedation and propose that it may have advantages over standard drugs in the sedation of hemodynamically unstable patients such as those recovering from myocardial infarction, endotoxemia, cardiomyopathy, or closed head injury. The use of a specially designed closed-circuit ventilation system minimized the cost while allowing routine tracheal suctioning and physiotherapy procedures to be performed.

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